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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/360,934	07/26/99	COVACCI	A	CHIR-0158

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EXAMINER	
BUI, P	
ART UNIT	**PAPER NUMBER**
1638	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/360,934	Applicant(s) Covacci et al.
	Examiner Phuong Bui	Group Art Unit 1638

☒ Responsive to communication(s) filed on Aug 7, 2000 .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 38-40, 42, 43, 45, 46, and 48-52 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 38 is/are allowed.

☒ Claim(s) 39, 40, 42, 43, 45, 46, and 48-52 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) 08/256,848 .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of amendment C, Paper No. 9, and the unexecuted declaration of Giuseppe Del Giudice under 37 C.F.R. 1.132, filed August 7, 2000. Claims 41, 44 and 47 have been canceled. New claims 51 and 52 have been entered. Claims 38-40, and 42, 43, 45, 46, and 48-52 are pending and are examined in the instant application. This action is made FINAL.

Information Disclosure Statement

2. An initialed copy of Applicant's Form PTO-1449, filed February 22, 2000 (Paper No. 4) is attached to this Office action. However, since a copy of the Figura et al. document was not submitted, this document has not been considered.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

4. Applicant's correction of the continuity data and insertion of SEQ ID NOs in the specification have been entered. The Abstract has been entered. Accordingly, the objection to the specification set forth in the previous Office action, Paper No. 3, mailed February 7, 2000, has been overcome by Applicant's corrections.

Sequence Compliance

5. Applicant's sequence submission of August 7, 2000 is compliant and has been entered.

35 U.S.C. 112, second paragraph

6. The rejection of claims 40-50 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been overcome by Applicant's response. In accordance with the meaning recited on page 8 of the response, "substantially reduced functional contribution to toxicity" and "substantially no toxicity" will both be read to mean "does not exhibit statistically significant cytotoxic effects".

7. Claims 39, 40, 42, 43, 45, 46, 48-50 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims recite the phrase "at least about" in setting forth the limitation as to the minimum length of the fragment. This phrase renders these claims indefinite in accordance with MPEP 2173.05(b)(A.) and Amgen v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Here there is close prior art, Cover et al., who teaches the CT protein from *Helicobacter pylori*. Further, there is nothing in the specification, prosecution history, or prior art that indicates what range of specificity is covered by the term "about". Accordingly, this phrase renders indefinite each of the claims in which it is used.

35 U.S.C. 112, first paragraph

8. The new matter rejection of claims 40-50 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been overcome by Applicant's response.

9. Claims 43, 45, 46, 48-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *H. pylori* cytotoxin and non-toxic immunogenic fragments thereof, does not reasonably provide enablement for "prophylactic or therapeutic vaccine" recitation in the claims, nor methods for making and using this vaccine. The basis for this rejection was set forth in the previous Office action, Paper No. 3, mailed February 7, 2000.

The Declaration of Giuseppe Del Giudice under 37 C.F.R. 1.132 filed August 7, 2000 has been fully considered, but was not found persuasive. Initially, the Office notes that this Declaration was not executed. Though Applicant indicates in their response that an executed copy would be later forwarded to the Office, no such copy has yet been matched with the application. However, since Applicant indicates that a signed copy will be forthcoming and Applicant reiterates the points made in the Declaration in their response, the Office has considered the merits of the as-yet-unsigned Declaration in order to expedite prosecution. Applicant is required to, in response to this Office action, submit a properly executed copy of the Del Giudice Declaration.

Applicant should note that the Declaration was found persuasive to the extent that determination of immunogenic fragments that were also non-toxic would have been within the skill in the art at the time of filing. However, with regard to determination of vaccine efficacy, especially for prophylactic administration, the Declaration was unpersuasive in that the showings set forth therein are not commensurate in scope with the specification.

Declarant asserts that animal models for the study of infection were known prior to the March 2, 1992 filing date of Applicant's Italian priority document. Declarant also establishes the existence of immunological assays to screen for antibody production in response to immunizations with CT protein fragments. For the record, the Office avers to the existence of animal models for the study of *H. pylori* infection and to the existence of immunological screening assays for determining immunogenic fragments. Further, the Declaration establishes that determination of non-toxic, immunogenic fragments of the CT protein was well within the skill and knowledge of the art at the time of invention.

Nonetheless, the existence of animal models does not in itself support Declarant's conclusion that these animal models would allow or enable determination of prophylactic or therapeutic effect to be routinely carried out with a reasonable expectation of success. Such a conclusion is unsupported on the record for the following reasons Declarant's Exhibit E reviews animal models of *H. pylori* infection and their use in vaccine studies. This exhibit actually contradicts Declarant's conclusion. On pages 247 and 248, section 2.8.3, the author indicates that the initial assumption in *H. pylori* studies was that gastric IgA antibodies probably played a

major role in preventing or clearing *H. pylori* based on knowledge from other mucosal pathogens. The author continues by stating that protection from *H. pylori* can actually occur in the absence of any antibodies, indicating that T-cells may play a role in protection from *H. pylori* infection. These two facts contradict Declarant's conclusion that vaccine studies were routine at the time of the invention, especially in light of the recent 1999 publication date of this review article. This problem would be present for both the full length CT protein and any non-toxic, immunogenic fragments thereof.

The fragments present an additional problem not seen in with the full length antigen. Even if Applicant were able to show that the full length antigen is capable of preventing or clearing *H. pylori* infection, discovery of the protective epitope or epitopes would still be highly unpredictable and involve extensive, undue experimentation. Although screening for linear epitopes was considered routine at the time of the invention, screening for non-linear epitopes was not. To discover non-linear epitopes, it is necessary to analyze the 3-dimensional structural conformation of the protein as well as its amino acid sequence. Moreover, many vaccines require multiple epitopes, and even multiple antigen types to provide protection. Thus, the discovery of protective epitopes is therefore highly unpredictable.

Exhibit G discusses vaccines using a detoxified form of the CT protein that provided significant clearance and protection in a mouse model. These vaccines included a mucosal adjuvant and included a detoxified form of the full-length protein. Exhibit H discusses vaccines which also provided significant clearance and protection in a dog model. These vaccines included

a mixture of cytotoxin VacA with a recombinant, full-length CagA protein and NAP in addition to aluminum hydroxide as the adjuvant. Administration was via intramuscular vaccination. Though these two references demonstrate the vaccine potential of the CT protein, they fail to support enablement of the claimed invention. Both references are post-filing documents. The use of post-filing documents cannot support enablement of a claimed invention unless the teachings of these documents follow the teachings of the specification. In this case, both references go beyond the teaching of the specification. Exhibit G uses a mucosal adjuvant. Exhibit H uses a mixture including NAP. Neither of these teachings was disclosed and is claimed by Applicant. Accordingly, these two documents fail to support enablement of the claimed invention, even with regard to a detoxified form of the full-length CT protein. Additionally, though the CT protein has been shown to have vaccine potential, neither document provides any support whatever for protective non-toxic, immunogenic fragments within the scope of the claims.

Applicant's response filed August 7, 2000 has been fully considered, but was not found persuasive. Applicant asserts that there is insufficient evidence to support this rejection. In accordance with the 35 U.S.C. 112, first paragraph, enablement guidelines of August 1996, evidentiary support for such a rejection may be provided in either references or scientific reasoning. To the extent that this rejection was founded on scientific reasoning, the references now submitted by Applicant in support of the 37 C.F.R. 1.132 Declaration in fact bear out this reasoning. For example, the previous action indicates that a mucosal adjuvant is required for vaccine efficacy of *H. pylori* component vaccines. In Exhibit G, the inventors with others

administered a CT protein in admixture with a known mucosal adjuvant via a mucosal route of administration. As was already discussed above, Exhibit F, a 1999 review article, indicates that "[b]ased on knowledge from other mucosal pathogens, the initial assumption in Helicobacter vaccine studies was that gastric IgA antibodies probably played a major role in preventing or clearing *Helicobacter* infections." (Exhibit F, page 247, section 2.8.3). Exhibit H confirms this approach on page 5, lines 30-32 to page 6, lines 1-12. Exhibit H filed by the instant assignee, indicates that a systemic protective effect against *H. pylori* infection can be "unexpectedly" achieved used a non-mucosal route of administration and a non-mucosal adjuvant (Exhibit H, page 6, lines 13-20). Thus, the effects of *in vivo* administration were poorly understood until recently, and certainly at the time of the filing of this invention.

Finally, the Office declines Applicant's request for an affidavit under 37 C.F.R. 1.104(d)(2), as such is not deemed necessary given the current record.

35 U.S.C. 102

10. The rejection of claims 38-49 under 35 U.S.C. 102(a) as being anticipated by Applicant's admitted prior art Cover et al. has been overcome by Applicant's amendment requiring that the CT polypeptide is non-toxic.

Remarks

11. Claim 38 is allowable. Claims 39, 40 and 42 would be allowable if rewritten to overcome the rejection under 35 U.S.C. 112, second paragraph above. The prior art fails to teach or

suggest either a detoxified form of the CT protein or an immunogenic fragment thereof that is also non-toxic.

12. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers relating to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638, using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Bui whose telephone number is (703) 305-1996. The Examiner can normally be reached Monday-Friday from 6:30 AM - 4:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Phuong Bui
Patent Examiner
Group Art Unit 1638
November 4, 2000

PHUONG T. BUI
PRIMARY EXAMINER